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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,466	01/26/2004	Sachiko Machida	690115.401C1	8356

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EXAMINER	
YU, MELANIE J	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,466	MACHIDA ET AL.	
	Examiner	Art Unit	
	MELANIE YU	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 25 April 2008 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holtzman (US 5,969,123) in view of Schatz (US 5,932,433) further in view of Tall et al. (US 6,756,228).

Holtzman teaches a biochip for a screening assay (col. 12, lines 7-8) comprising a biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin (streptavidin specifically binds to biotin and the biotinylated proteins is immobilized to the streptavidin, col. 12, lines 8-16), wherein the receptor protein comprises a biotinylation sequence motif (biotinylated protein comprises biotinylation sequence motif, col. 12, lines 11-16), and wherein the receptor protein has the ability of

being specifically bound by a ligand of the receptor protein (col. 8, line 65-col. 9, line 6). Holtzman fails to teach the biotinylation of the receptor protein carried out within a bacterial host and the receptor specifically being LOX-1.

Schatz teaches a recombinantly expressed biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin (peptides are biotinylated and bound to streptavidin which specifically binds to biotin, col. 8, lines 10-27, biotinylated peptide may be a protein, col. 6, lines 13-19), wherein the receptor protein comprises a biotinylation sequence motif (when peptides are biotinylated, they gain a biotinylation sequence motif, col. 8, lines 10-27; col. 4, lines 57-60), wherein the biotinylation of the receptor protein has been carried out within a bacterial host instead of in vitro (carried out in *E. coli* host cells, col. 3, lines 47-50; col. 8, lines 10-14), in order to provide a protein that has been biotinylated.

Tall et al. teach a LOX-1 receptor immobilized to a substrate (col. 12, lines 29-38; col. 11, line 52-col. 12, line 57) wherein the LOX-1 receptor binds to an endogenous ligand (oxidized-LDL, col. 11, lines 39-51), in order to detect the presence of LOX-1 activity.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the biotinylation of the receptor protein of Holtzman, biotinylation in vivo instead of in vitro as taught by Schatz, in order to provide a simplified biotinylation process (Schatz, col. 2, lines 59-63). It would have further been obvious to one having ordinary skill in the art at the time the invention was made to include as the receptor protein of Holtzman in view of Schatz, a receptor protein of

LOX-1 as taught by Tall et al., because Holtzman is generic with respect to the immobilized receptors that can be incorporated into the chip and one having ordinary skill in the art would be motivated to use the appropriate receptor ligand for detection of a desired analyte and to indicate increased or decreased susceptibility to atherosclerosis. Although Holtzman in view of Schatz further in view of Tall et al. fail to specifically teach the immobilized receptor protein obtained by refolding a biotinylated receptor protein expressed as an inclusion body within the host, such a limitation is drawn to a method of making the protein on the chip. The instant claims encompass a product of the receptor chip and not a method of making the product, the LOX-1 immobilized on the chip as taught by the prior art must be the same receptor protein required by the claims. Since the combination of prior art references described above, teaches a LOX-1 receptor protein biotinylated in a bacterial host and then immobilized on the substrate via the biotinylation sequence motif, the combination of the prior art references teaches the required structural limitations of the claim and the LOX-1 protein of the prior art reads on the claimed LOX-1 protein.

3. Claims 17 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brigham-Burke et al. (US 5,395,587) in view of Holtzman (US 5,969,123) further in view of Schatz (US 5,932,433) and Tall et al. (US 6,756,228).

Brigham-Burke et al. teach a protein immobilized on a SPR substrate (sensor chip, col. 5, lines 29-35; col. 5, lines 10-23) that conforms to a shape of an insertion site of a surface plasmon resonance device (sensor chip fits through a slot in the housing for

SPR detection, 14, Fig. 1; col. 5, lines 30-35), but fail to teach the protein being biotinylated and immobilized via a factor capable of binding specifically to biotin.

Holtzman in view of Schatz further in view of Tall et al., as applied to claim 1, teach a biotinylated receptor protein immobilized on a substrate via a factor capable of specifically binding to biotin, in order to provide immobilization of receptor proteins on a substrate.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the substrate of Brigham-Burke et al., an immobilization technique of a biotinylated receptor protein as taught by Holtzman in view of Schatz further in view of Tall et al., in order to simple and efficient immobilization of proteins on a substrate.

4. Claims 17 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muramatsu (Piezoelectric Crystal Biosensor Modified with Protein A for Determination of Immunoglobulins, 1987, Analytical Chemistry, vol. 59, pages 2760-2763) in view of Holtzman (US 5,969,123) further in view of Schatz (US 5,932,433) and Tall et al. (US 6,756,228).

Muramatsu teaches a protein immobilized on a crystal oscillator (pg. 2760, right column, last paragraph), but fail to teach the protein being biotinylated and immobilized via a factor capable of binding specifically to biotin.

Holtzman in view of Schatz further in view of Tall et al., as applied to claim 1, teach a biotinylated receptor protein immobilized on a substrate via a factor capable of

specifically binding to biotin, in order to provide immobilization of receptor proteins on a substrate.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the substrate of Muramatsu, biotinylation of a protein receptor and immobilization via a factor capable of binding specifically to biotin as taught by Holtzman in view of Schatz further in view of Tall et al., in order to simple and efficient immobilization of proteins on a substrate.

Response to Arguments

1. Applicant's arguments filed 25 April 2008 have been fully considered but they are not persuasive. At page 5, applicant argues that non-glycosylated LOX-1 of the present invention binds to both AcLDL and OxLDL, typical endogenous ligands and the binding constant between the endogenous ligands and LOX-1 is comparable to the dissociation constant of LOX-1 expressed on a cell surface. Applicant argues that the results of an immobilized LOX-1 protein binding to its endogenous ligand in the instant claims was surprising and therefore the prior art does not anticipate the combination. Applicant's arguments are not persuasive because Tall et al. teach an immobilized LOX-1 receptor binding to the endogenous ligand of OxLDL, and therefore the LOX-1 of the rejected claims and LOX-1 of Tall et al. have the same binding capabilities and the binding of the prior art LOX-1 to OxLDL would be expected. The claims do not specifically recite and non-glycosylated LOX-1 receptor.

2. At pages 5-7, applicant argues that in the prior art, it was known that non-glycosylated LOX-1 has substantially reduced binding affinity and therefore a skilled

artisan would not believe that a recombinantly produced LOX-1 polypeptide would have the ability to bind an endogenous ligand when immobilized on a chip. Applicant's argument is not persuasive because Tall et al. teach an immobilized LOX-1 receptor that binds to an endogenous ligand that is OxLDL. One having ordinary skill in the art would have a reasonable expectation of success in combining these references because Holtzman teaches a biotinylated receptor (recombinantly produced) immobilized on a substrate and retaining its ability to bind to a ligand. Therefore one having ordinary skill in the art would expect a recombinantly produced LOX-1 receptor to retain its affinity to an endogenous ligand. Furthermore the instant claims do not specifically require and glycosylated or non-glycosylated LOX-1 receptor.

3. At page 6, applicant argues that none of the cited references demonstrate substantial binding between non-glycosylated recombinantly produced LOX-1 protein to endogenous ligands. Applicant's argument is not persuasive because the rejected claims do not require the LOX-1 protein to be non-glycosylated. Furthermore, the combination of Holtzman, Schatz and Tall et al. teach an immobilized biotinylated LOX-1 receptor that binds to OxLDL, which is an endogenous ligand.

4. In response to applicant's argument, at page 6, that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Holtzman teaches an assay with an immobilized biotinylated protein, Schatz teaches biotinylation of a receptor protein carried out within a bacterial host which provides a simpler biotinylation process than that described by Holtzman. Furthermore, Tall et al. teach a receptor protein of LOX-1, wherein the motivation to combine with Holtzman and Schatz is to provide a receptor protein that is specific for a desired analyte of interest and to indicate increased or decreased susceptibility to atherosclerosis.

5. At page 7, applicant argues that the cited references do not suggest that a LOX-1 receptor can be successfully adapted to *in vivo* biotinylation and expression protocols and there would be no reasonable expectation of success in arriving at the claimed subject matter or expectation of biotinylated mammalian LOX-1 produced from inclusion bodies in bacteria to correctly re-fold and bind its ligand. Applicant's argument is not persuasive because Holtzman teaches immobilization of a biotinylated protein receptor (which has been biotinylated *in vitro*) on a substrate, Schatz teaches the biotinylation of a receptor protein *in vivo* instead of *in vitro* and Tall et al. teach that a receptor protein of LOX-1 may be immobilized on a substrate. One having ordinary skill would have a reasonable expectation of success in combining these references because Holtzman teaches immobilization of a receptor biotinylated *in vitro* on a substrate. Schatz teaches that a receptor may be biotinylated in a bacterial host *in vivo* instead of *in vitro*. Tall et al. teach that a LOX-1 receptor may be immobilized on a substrate to bind an endogenous ligand (Oxidized-LDL). Applicant argues that one having ordinary skill

would not have expected the combination of Holtzman, Schatz and Tall et al., but does not provide substantial evidence as to why the combinations of references would not work. One having ordinary skill would be motivated to combine the references with a reasonable expectation of success because the immobilized biotinylated receptor of Holtzman retains its binding properties and therefore a skilled artisan would expect the LOX-1 receptor taught by Tall et al. to also retain binding properties with OxLDL. Schatz is relied upon for an easier biotinylation technique, and teaches *in vivo* or *in vitro* biotinylation which one having ordinary skill would expect to be functional equivalents and therefore would not alter the binding properties of the receptor.

6. At pages 7-8, applicant argues that the claimed receptor chip provides unexpected advantages over the prior art because the instant application attains significant effects in terms of detection of extremely low concentrations of endogenous ligands and the sensitivity would not be expected by those skilled in the art. Applicant's argument is not persuasive because applicant provides no results or evidence of comparison between the *in vivo* biotinylated LOX-1 receptor of the prior art and the claimed LOX-1 receptor to show that increased sensitivity exists. Furthermore, the combination of references teaches the claimed biotinylated LOX-1 receptor and therefore has the same properties as the claimed LOX-1 receptor.

7. At page 8, applicant argues that the references of Brigham-Burke et al. and Muramatsu teach producing a receptor chip comprising a LOX-1 protein having a high affinity to endogenous ligands. Applicant's argument is not persuasive because Bringham-Burke and Muramatsu are not relied upon for teaching these limitations.

Conclusion

8. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELANIE YU whose telephone number is (571)272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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